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Pharmaceuticals and Personal Care Products in the Environment

Letter to the Editor

Chemicals from the Practice of Healthcare: Challenges and Unknowns Posed by Residues in the Environment

The practice of healthcare often relies heavily on the use of a bewildering array of chemicals for diagnostics, therapy, prophylaxis, and lifestyle/cosmetic modification. Excretion, bathing, manufacturing, and disposal of pharmaceuticals and personal care products (PPCPs) serve as conduits to the environment for complex mixtures of parent chemicals and transformation products, primarily via sewage and domestic refuse. As members of a much larger universe of natural products and other anthropogenic chemicals that already pervade the environment, PPCPs enter the environment primarily from multitudes of individually miniscule sources. Each source by itself contributes relatively insignificant quantities but the combined inputs can yield measureable levels in waters and other environmental compartments, with the general exception of air. Scenarios abound for chronic, low-level ambient exposure of wildlife, microbiota, and humans but special situations can lead to higher-level, acute exposures. Whatever the existing risks, they can span a wide spectrum of modalities and can be difficult to decipher because of the complexities posed by simultaneous exposures to numerous chemical stressors - perhaps each present below any individual level known to perturb biological processes - and some leading to difficult-to-detect or delayed-onset subtle effects.

The study of PPCPs in the environment (PiE) has proved challenging over the course of the last 15 to 20 years of international research. Significantly, the ultimate aims of PiE research are sometimes unclear. Overall priorities need to be established to achieve outcomes that still remain to be articulated. While the published scientific literature has grown to thousands of papers targeted primarily at deciphering the shape, scale, intensity, and spatiotemporal aspects of the environmental footprint, exposure envelope, and potential for biological effects of PPCPs, many aspects of PiE remain obscure. Given the possible reality of continually diminishing resources for research, a concerted effort is needed to identify those select aspects capable of removing the most uncertainty in assessing whatever risks might be posed by PiE; target those aspects having the highest potential to broadly benefit human health and the environment; and better coordinate and focus future research.

The study of PiE is notable in that it requires expertise spanning a remarkably diverse spectrum of disciplines - ranging from hydrology, civil engineering, and chemistry, to pharmacology, toxicology, medicine, and even social psychology and risk communication. Study of PiE has captured the attention of not just scientists, but also policy makers, legislators, regulators, environmental agencies, healthcare communities, public, press, and the pharmaceutical, pharmacy, and health insurance industries. It has also slowly morphed into the much larger issue of the so-called but loosely defined "emerging contaminants" - a catch-all term for contaminants whose presence or significance was previously unknown, unrecognized, or underappreciated [1].

Why does PiE persist as a topic of interest for so many? A major reason is that despite the accelerating pace of published investigations, new questions continue to be generated while some major ones remain unanswered. Moreover, the fact that PPCPs (a term coined 10 years ago [2]) occur in waters serves to illustrate the intimate connections between the activities and behaviors of humans and the environment - a continual reminder of the hydraulic connectivity between sewage and "natural" waters. They remind each of us that we are integral parts of the water cycle. Their seeming ubiquity in waters, especially potable waters, serves as a constant (and sometimes emotional) reminder that these waters originated at least in part from the excretions of others – from feces, urine, and sweat [3]. This factor certainly looms large with the life cycle of PPCPs and can play a critical role in the public acceptance of water reuse.

Pharmaceuticals and personal care products comprise thousands of distinct chemical entities and tens of thousands of commercially formulated products, possessing an immense range of physicochemical and physiological properties. For drugs, each active pharmaceutical ingredient (API) can be assigned to one of many therapeutic groups, such as those of the tiered Anatomic Therapeutic Chemical (ATC) Classification system or the analogous system for veterinary medicines (e.g., see discussion in Table 5 of Ruhoy and Daughton [4]). Because of the extreme diversity of PPCPs (especially their wide range of biochemical activities), generalizations applied across the entire spectrum (or even within defined classes) are prone to misrepresentation and numerous exceptions. Even broad classes sharing the same therapeutic modalities (e.g., lipid regulators [ATC C10] or antidepressants [ATC N06A]) can act via a wide

variety of biochemical routes. Despite these categories of therapeutic action, actual mechanisms of action are frequently unknown and individual APIs can be promiscuous in their biochemical actions.

Among the reference citations in the U.S. Environmental Protection Agency's (U.S. EPA) bibliographic database on PPCPs (http://www.epa.gov/ppcp/lit.html), publications with a focus on personal care products comprise a much smaller portion (about 10% of the total) than do APIs. The major personal care product groups that have been investigated are the synthetic musks, triclosan/triclocarban, ultraviolet filters/sunscreens, parabens, and siloxanes, in decreasing order of prevalence in the literature. Phthalates, bisphenol A, and nonylphenols are involved with higher numbers of publications but their usage in personal care is minor compared with other commercial uses. In general, the active agents in the thousands of commercial formulations of personal care products are produced and consumed in much larger quantities than APIs but their biological potencies are also much lower.

Nearly all aspects of APIs in the environment have parallels for both human and animal pharmaceuticals; indeed, many APIs have dual uses. The relative importance, however, of these aspects among human and animal applications can differ greatly because of the dominance of (and special needs imposed by) confined animal feeding operations in the overall use of APIs targeted for animals, where antibiotics and the endogenous and synthetic steroids play dominant roles. The focus of roughly 10% of the articles inventoried in the U.S. EPA bibliographic

97 database on PPCPs is veterinary and aquaculture usage. Perspectives on the roles of veterinary
98 medicines as environmental contaminants have been covered in a number of excellent reviews,
99 including those published in Crane et al. [5].
100
101 **Many Challenges – but Which Are Most Important?**
102 Environmental scientists and healthcare professionals face nearly endless challenges with
103 PPCPs. But which of these challenges leads to valuable near- and long-term outcomes that
104 protect and improve human health and ecological function? We must also determine where
105 PPCPs fall within the growing list of overarching environmental issues in a world of diminishing
106 resources and continually emerging new concerns.
107
108 The issues and concerns surrounding PiE involve the interface between humans and the
109 environment – where the everyday individual actions, activities, and behaviors of multitudes of
110 people combine and intersect with the environment via dynamic transfer and recycling of
111 countless different chemicals, most of which were designed to impart biological effects.
112 Targeting of research will require integration of knowledge regarding the presence, fate, and
113 effects of PPCPs in the environment with what is known about the countless sources and origins
114 of their release as a direct result of the management and administration of healthcare. A key
115 insight into this challenge is that a wide spectrum of actions targeted at reducing the transfer of
116 PPCPs to the environment holds the potential for reciprocally improving the quality and costs of
117 healthcare [6]. Treating the environment and healthcare as an integral system could greatly

clarify where and how to invest resources to achieve optimal outcomes, as improvements in either can lead to collateral improvements in the other.

Using prioritization tools such as multi-criteria decision analysis (MCDA) coupled with value of information (VOI), and examining the continuum of steps spanning the risk paradigm - beginning with sources and origins and ending with biological effects and risk management - could be used to establish relative priorities; for examples of this process, see Kiker et al. [7] and Linkov et al. [8]. Nearly every stakeholder involved with PiE serves not only as an interested party, but also as an actual contributor to some aspect of the overall problem, as well as a potential beneficiary from solutions. Each stakeholder also can play an active role as problem solver; the physician can alter prescribing habits, the consumer can make more prudent purchases and properly dispose of leftover drugs, and the insurer can encourage dispensing of prudent quantities. To identify the relative importance of each modification needed to improve a system as large and complex as health care requires establishing clear priorities, which in turn must be based on quality data.

A Large but Under-Utilized Base of Knowledge

Of the 7,000 or so references currently captured in the U.S. EPA bibliographic database on PPCPs (over 85% of which are articles from journals or books but largely omitting the non-English literature), over 90% have been published only since 1999 **(*Supporting Information*, Fig. S1; http://dx.doi.org/10.1897/09-138.S1)** . The international extent of the

topic is evident from the numbers of publications that feature a particular country in the abstract or title. Over 1,600 articles mention 10 different countries (Australia, Britain, Canada, China, Europe, Germany, Italy, Japan, Spain, and Sweden) and Europe, and over 600 mention the U.S. Of 150 academic dissertations, 60% are from outside the U.S. Of the seven most highly cited papers on PiE, five originated in Europe and two from the U.S.

While this certainly shows an ongoing escalation in publishing activity, it does not tell us if these works have targeted the most pressing needs, if they are being actively used to inform decision making, or whether they are resulting in useful outcomes for society. Moreover, if one were to assume an extremely conservative cost of merely US$10,000 to $100,000 per paper, the last 10 years of research targeted toward PPCPs may have consumed minimum resources roughly upwards of US$600M. Such a substantial investment prompts the question of whether these resources could have had more productive outcomes or greater impact if they had been invested elsewhere in the field of PPCPs or, perhaps more significantly, even elsewhere in environmental sciences at large? Perhaps not surprisingly, the impressive wealth of data published on the topic of PiE has generated a host of new questions, which, paradoxically, can serve to breed yet more uncertainty. At the same time, however, the new knowledge gained for PPCPs is often directly relevant to other types of chemical contaminants, serving to leverage resources throughout the environmental sciences arena.

Two overarching concerns for PiE have centered on human health risk and ecological integrity, especially aquatic effects from the perpetual entry of residues via sewage (pseudo-persistence). The ultimate destination for PiE research might be evident only in the larger context involving a truly holistic examination of PiE and the complete life cycles of PPCPs. Can healthcare systems and the manufacturing and distribution of PPCPs be designed and optimized to leave a minimal environmental footprint? The argument has been made that in taking actions to reduce and ultimately minimize an ill-defined hazard (namely, the release of PPCPs to the environment) by reinventing healthcare administration and delivery of health care, improvements in therapeutic outcomes might follow naturally, together with reductions in the costs associated with medical care [6].

The best outcomes regarding release to the environment might emerge from optimizing the way in which health care and personal care are administered, distributed, prescribed, dispensed, and employed and how PPCPs are designed and produced. Reactive approaches using end-of-chain controls are not as efficient or effective as proactive solutions that optimize source reduction or pollution prevention. By focusing on less sustainable end-of-pipe solutions, such as improved ways to dispose of unwanted medications or more efficient treatment of wastewaters, approaches with even better outcomes might escape consideration. As one example, consider that the imprudent usage of PPCPs coupled with the extent of leftover medications can be viewed as direct measures of the inefficiencies and wastefulness that can occur along the entire lifecycle of PPCPs. Leftover medications represent much more than just chemical wastes needing disposal.

They represent wasted healthcare resources, inflated and unnecessary consumer expense, and missed opportunities for achieving optimal therapeutic outcomes [6]. By focusing on controlling the many causes leading to the accumulation of unwanted medications, not only would the need for disposal be reduced, but excretion and discharge of residues of PPCPs might also be incidentally reduced as a result of optimized usage. Such holistic approaches require the involvement of specialists from fields that may not have foreseen ever playing active roles in the PiE issue.

Key to Reducing PiE's Footprint

In the early 1920s, Henry Ford conceived of a new strategy for inventory maintenance designed to improve return on investment. Called just-in-time (JIT), this new paradigm redefined on-hand inventory as essentially being the equivalent of waste. Optimal performance meant perfect balance between demand and on-hand supply. If a JIT perspective were applied to healthcare, medication waste could be viewed not just as additional chemical contaminant burden for the environment, but more importantly as a prime metric of inefficient, non-optimal administration of health care. Redesign of health care using the JIT perspective and the knowledge and expertise of medical practitioners, healthcare administrators, pharmaceutical manufacturers, and environmental scientists could lead to a holistic system of balanced and optimally targeted delivery of medical care. Such a system could yield improved therapeutic outcomes, lowered costs, and reduced environmental impact.

The effectiveness of efforts directed at pollution prevention or source reduction increase as the targeted steps reside closer to the source or origin of the chemical. Tracing the ultimate origin back to chemical design, advancements in eco-design could prove to have significant outcomes not only in reducing environmental impact, but also in improving healthcare outcomes ([6, 9] ; http://www.mistrapharma.se/program/mistrapharma/home/pressandmedia/newsarchive/news/releaseparty.5.75aa40e311fe8049dfc8000176.html).

In the near term, consideration could be given to the design of pilot projects designed around stewardship actions in healthcare. Healthcare organizations having control over all aspects of medical care might serve as excellent testing grounds for pilot projects; in the U.S., one example for testing new approaches could be the nation's largest integrated healthcare system - the Veterans Health Administration.

Framing a Bigger Picture

Despite the thousands of publications devoted to the many facets of PiE, unanswered questions persist and continue to proliferate. Many of these questions, however, are also germane to some of the major issues that permeate environmental science as a whole rather than being critical to solving specific problems associated solely with PiE. Significantly, despite the wealth of published data, little has yet proved of use in actual implementation of system redesigns that are more sustainable or even for informing regulatory deliberations regarding PiE.

A major weakness in the application of environmental science to PiE has been the failure to frame the issue in a much larger context - using a “systems” approach that involves experts from fields other than primarily just analytical chemistry and environmental engineering. A comprehensive, international strategy for tackling PiE using a harmonized approach integrated

across a spectrum of disciplines could also involve social psychologists and risk communicators, physicians, pharmacologists, pharmacists, drug designers, and health insurers.

Once the PiE issue is successfully framed in a larger, holistic context having meaning to a broader audience, and collaborations are established among those from across disparate disciplines, more productive outcomes could possibly emerge. The requisite framing must show how health care and personal care can lead directly to environmental contamination. But more importantly, clear communication would be essential for how measures directed at redesigning their administration to minimize the PiE footprint can in turn improve the affordability and desired outcomes from the consumer use of PPCPs. Required actions could become clearer and more readily embraced when considering the patient and the environment as an interconnected whole.

Although voluminous published and gray literatures exist for PiE, a large number of gaps remain that could be investigated [10]. Science is never short on questions. More important to address first, however, is what exactly do we wish to accomplish with more research? What outcomes are we seeking? How would the uncertainty associated with assessing risk be most efficiently minimized? Closer collaboration between researchers and risk assessors would be highly beneficial. Most importantly, however, the concerns, challenges, and solutions regarding PiE need to be framed and examined in the expanded context of the larger systems used for the care of human and animal health.

In the table (***Supporting Information*, Table S1; http://dx.doi.org/10.1897/09-138.S2**), some notable gaps and unresolved questions are compiled, and examples are provided to illustrate a range of issues that might be considered for further attention and discussion. The following introduces these questions and concerns.

Interconnectedness and unintended consequences

Solutions that might seem at first to solve a certain problem can have unintended, and sometimes adverse, consequences. The interconnectedness of our world might seem obvious from our vantage point today, and it is certainly embodied in the new "systems" disciplines. But the realization that "everything is connected to everything else" was first formalized less than 40 years ago (in 1971) by Barry Commoner - as his "First Law of Ecology." Garrett Hardin later reformulated the idea in "we can never do merely one thing" (Hardin's Law). That unanticipated or unforeseeable outcomes can result from a single action was captured by what Crawford Holling later called "environmental surprise," where the ultimate outcome can differ dramatically from what was anticipated. But the forerunner to the modern environmental movement was George P. Marsh, who, over 150 years ago, recognized that interconnections pervade all of nature: "No atom can be disturbed in place, or undergo any change of temperature, of electrical state, or other material condition, without affecting, by attraction or repulsion or other communication, the surrounding atoms. These, again, by the same law, transmit the

influence to other atoms, and the impulse thus given extends through the whole material universe" [11]. Some examples of unanticipated consequences pertinent to PiE are provided in Table 1.

Mining the published PiE literature

Multi-criteria decision analysis and VOI could serve as the principal means for setting PiE priorities. A number of areas on face value seem to deserve concerted attention. Many have been delineated in publications and various government reports. A primary need is to capitalize on what is already available - the published literature, which could contain a wealth of data not yet examined and certainly never thoroughly mined, compiled, summarized, evaluated, and distilled into useful insights and knowledge. This is largely because synoptic reviews and compilation of prior data are generally not valued in science as much as the publication of new data. But given the uncertainty as to the extent these published findings have been evaluated (evidence exists that much of the published literature in general has never even been read [12]), the value of publishing without clear outcomes in mind must be questioned. This prompts the more general questions of how the impact of publishing can be improved, and how do we encourage the capture and synthesis of this hidden knowledge?

An examination of the U.S. EPA bibliographic database on PPCPs reveals that publishing on the topic of PiE began in earnest around 1996, which saw roughly twice as many articles as in 1995

(80 versus 40). The very first publications devoted specifically to the topic of PiE, however, began to appear in the 1970s. One of the very first significant works came from Tabak and Bunch at the U.S. Department of the Interior [13] followed six years later by Coats et al. [14]. The topic began to attract more than a thousand publications per year beginning in 2007. The first two months of 2009 showed more publications (256) than in all of 1999 (207); in the first 6 months of 2009, over 800 documents have either been published or are in press. A rapidly inflating literature (but not necessarily expanding in scope) greatly increases the possibility that an ever greater share of these publications will not receive adequate examination, as no longer can a single individual commit sufficient time to being thoroughly familiar with the literature as a whole; specialization in individual aspects of the topic is necessitated, and this can slow advancements in the absence of well-targeted cross-disciplinary collaborations. The lack of sufficient synoptic review greatly increases the risk of duplication of prior work and in not focusing new work where the highest priority gaps might be. Some additional aspects of literature mining are summarized (***Supporting Information*, Table S1)**.

Notable gaps

Cursory examinations of the studies published to date hint that the majority of data appears to focus on environmental occurrence and monitoring and on treatability efficiencies for wastes and drinking water. At the other end of the spectrum significant areas have received surprisingly little attention. Some of the major ones are summarized (***Supporting Information*, Table S1).**

309

310 An important aspect of environmental monitoring or site characterization studies rarely
311 discussed is the veracity of structural identification of contaminant unknowns. Unknown is the
312 frequency with which PPCPs purportedly identified in environmental samples have undergone
313 structural confirmation. This potential weakness leads to a number of questions (***Supporting***
314 ***Information*, Table S1).**

315

316 **Challenges for Toxicology**

317

318 Bringing to bear ever-more advanced measurement methods, analytical chemists allow us to peer
319 into the shadows of chemical space with greater magnification and clarity. While this newly
320 discovered chemical landscape might be fascinating to explore and serves to further illuminate
321 the expansive universe of chemical stressor exposure, at the same time it poses greater
322 challenges for risk assessors. This is especially true with regard to one of the greatest problems
323 facing toxicology today – simultaneous/sequential chronic exposure to multiple chemical
324 stressors, each present at ever-lower individual concentrations. While baseline narcosis is
325 believed to be the most common mode of action at very low stressor concentrations, the
326 possibility of unique, unpredicted mechanisms of action (MOAs) cannot be ruled out, especially
327 since MOAs can change with exposure levels (multi-phasic dose-response) and receptors can
328 vary across taxa. Increasingly lower detection limits will pose greater challenges for assessing,
329 communicating, and ameliorating diminishing risks. And an inflating known universe of

potential chemical stressors will challenge the feasibility or sustainability of regulatory/compliance monitoring on a chemical-by-chemical basis.

At the other extreme, technological prowess in measuring the very small sometimes distracts or over-shadows the potential for unanticipated scenarios for overt toxicity caused by acute exposures and poisonings - not just unintended poisonings of humans and pets from leftover medications, but also poisoning of wildlife via previously unrecognized source/exposure pathways and even unrecognized or unappreciated MOAs. Can improved assessment of risk for PPCPs account for the possibility of unanticipated exposure scenarios or adverse outcomes? What additional knowledge is required to avoid the scale and consequences of acute-exposure incidents such as the mass poisonings of raptors and scavengers by pentobarbital or residues of non-steroidal anti-inflammatories such as diclofenac (and possibly quinolone antibiotics) remaining in carcasses from medicated domestic animals, or to predict the unexpected acute toxicity of APIs to certain non-target species?

Our environment extends beyond the confines of water, soil, and air. It also encompasses where we live and even our bodies themselves, where residues of countless chemicals are applied to or excreted from the skin and then transferred to other surfaces where others can then unknowingly be exposed [3]. Other scenarios for acute exposures therefore include inter-human contact (e.g., from high levels of APIs remaining on the skin after dermal application or excreted via the skin)

and human contact with excretions from medicated pets; these issues are particularly germane for therapeutic treatments using highly cytotoxic or hormonal drugs.

With respect to prioritizing APIs for in-depth study, little evidence supports an overriding importance of toxicological data derived from therapeutic doses or commercial production volumes or usage rates. Also needing consideration are other critical variables involved with the life cycles of APIs, such as pharmacokinetics (e.g., the extent to which an API is extensively excreted unchanged – or as metabolically reversible conjugates - via feces, urine, or sweat), delivery route, patient compliance (lower rates of compliance generate leftovers and the consequent need for disposal), potency, usage patterns leading to episodic releases, and an API's propensity for off-target promiscuity.

A major problem with studies of long-term, low-level ecological exposure is the ever-increasing challenge of deconvoluting the occurrence of what might first appear to be an adverse effect in a certain (sub)population from the effect's frequency of incidence as ambient background. The problem of tying effects to exposure is discussed further (***Supporting Information*, Table S1)**; this problem also underlies regulatory frameworks based on assessment of hazard for individual chemicals. Moreover, even if causality can be established, the next hurdle must be faced: determining if effects actually impart detrimental, irreversible changes at the organizational level of the population.

Other gaps and research needs can be summarized along the continuum of the risk paradigm, spanning the range from chemical stressor sources to biological effects and remediation [10]. With respect to the topic of drug stewardship, the unknowns surrounding sources and origins are particularly important (***Supporting Information*, Table S1)**.

Dogma Masquerading as Knowledge

As with any field of study, always present is a risk that opinions, beliefs, and biases can become codified as dogma. Vigilance is needed to evaluate the veracity of purported facts, especially when misinformation might be unwittingly used to inform decision making. Statements regarding PiE that may be based more on suppositions than facts and which might benefit from more investigation (***Supporting Information*, Table S1)**.

The Larger Perspective

A final point involves the key importance in establishing and communicating the full context in which PPCPs exist in the environment as potential stressors for biological systems. Their place in the larger universe of chemical stressors is essential to appreciate so that the public can develop a more accurate and meaningful perspective of chemical exposure in general and that optimally informed regulatory decisions can be formulated. Diminishing resources for research must be directed to the most significant contributors of environmental risk. Of course, the true picture of the relative toxicological importance of PPCPs can only be obtained by considering all hazards, including non-chemical forms of stress, such as electromagnetic, radiological,

biological, physical, thermal, noise, and emotional, among many others. This presents an enormous challenge – one that cannot yet be satisfactorily addressed – but should at least be continually maintained in the background of discussion and debate to ensure steady progress in eventually acquiring the ability to assess risk in a truly holistic manner.

In the mean time, we can at the very least accept the issue of PiE in the environment as an opportunity – as a driver for improving the efficiency and efficacy of the responsible contributory systems. By involving the many professional communities engaged in health care, sustainable systems can be designed that could yield substantive savings in healthcare resources, improved patient outcomes, and combined protection of human health and ecological integrity.

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SUPPORTING INFORMATION

Fig. S1. Yearly publications relevant to PPCPs.

Found at DOI: 10.1897/09-138.S1 (137 KB PDF).

Table S1. Surprises, questions, and framing a bigger picture regarding PiE.

Found at DOI: 10.1897/09-138.S2 (38 KB PDF).

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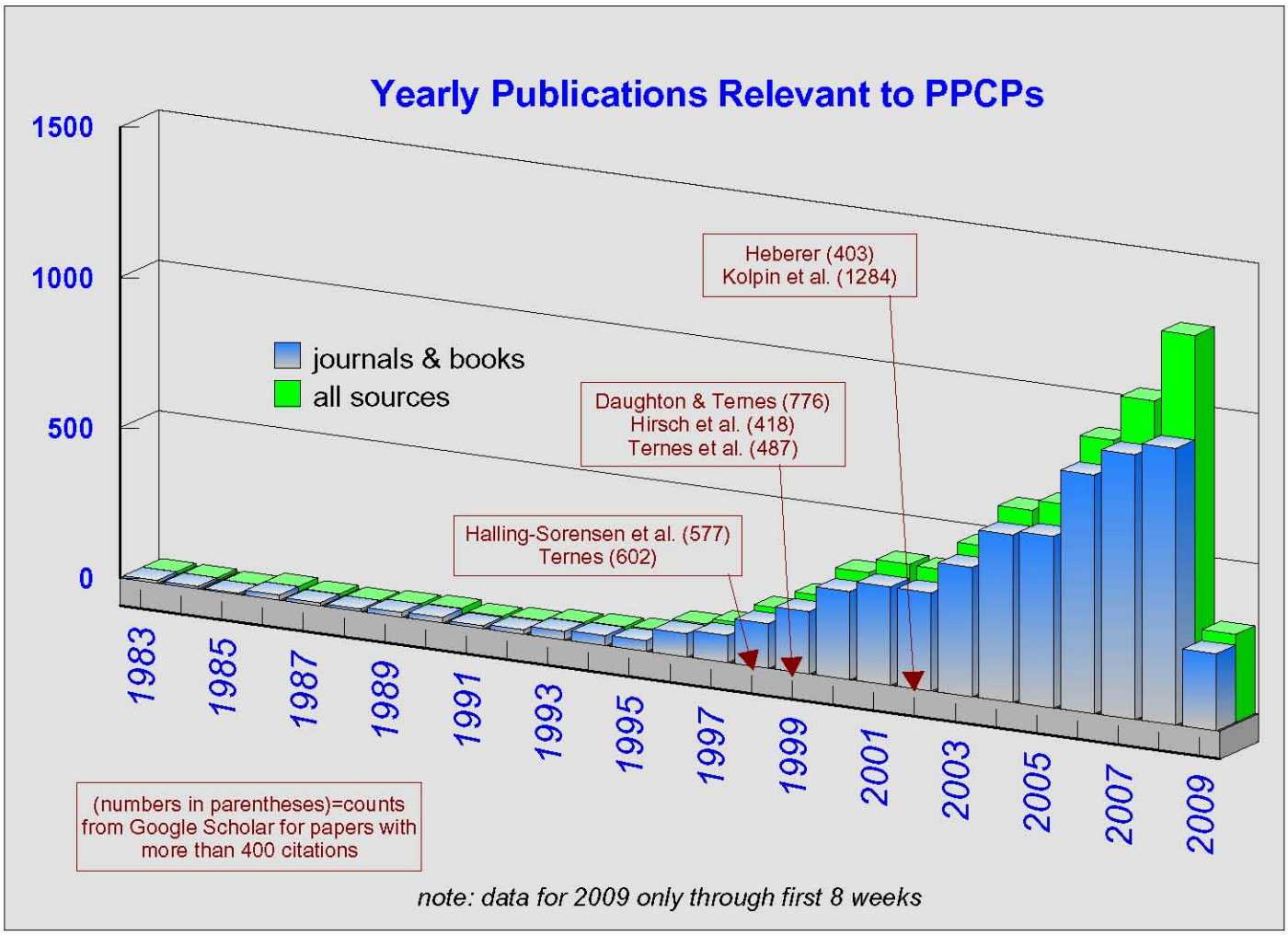
Yearly Publications Relevant to PPCPs
1500
1000
500
0
journals & books
all sources
Heberer (403)
Kolpin et al. (1284)
Daughton & Ternes (776)
Hirsch et al. (418)
Ternes et al. (487)
Halling-Sorensen et al. (577)
Ternes (602)
1983
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(numbers in parentheses)=counts from Google Scholar for papers with more than 400 citations
note: data for 2009 only through first 8 weeks

Table S1. Surprises, Questions, and Framing a Bigger Picture Regarding PiE

Surprises: Interconnectedness & Unintended Consequences	At times, an ultimate outcome can differ dramatically from what was anticipated. One example is the desire to eliminate the practice of flushing to sewers for the disposal of unwanted medications [1]. The most widely available disposal alternative in some countries such as the U.S. is discarding via the trash. Disposal to trash, however, can increase the diversion of drugs to others who should not be consuming them, facilitating drug abuse and exacerbating unintended poisonings, especially for children, pets, and scavengers [2]; the ultimate fate of APIs in landfills is also unknown. At the same time, the importance of disposal to sewers as a contributor to environmental residues is not known. Its contributory role, however, is likely a function of each individual API - perhaps being important for a limited set of APIs (mainly those that are ordinarily extensively metabolized) but unimportant for most others, especially those that are extensively excreted unchanged [3]. By avoiding the flushing of unwanted drugs into sewers could human morbidity and mortality perhaps be exacerbated? These unknowns serve to demonstrate that the ultimate objective might not be to determine the relative contributory role of disposal in the occurrence of PPCPs in the environment, but rather to design systems that result in eliminating the need for disposal in the first place, an undertaking requiring the efforts of all sectors of health care. While the focus on drug disposal has been primarily on consumers, the healthcare industry is also beginning to examine its practices; see the US EPA's efforts targeted at unused pharmaceuticals in the health care industry under the Effluent

	Guidelines Program (http://www.epa.gov/guide/304m/#hsi). The analogous situation exists for other unknowns surrounding the PiE footprint puzzle. For example, does research to determine if treatment technologies for wastewater or drinking water are effective for PPCPs and how treatment can be improved even need to be justified by whether PiE contamination poses known risks? Could the problem instead be reframed by looking at PPCPs as proxies for portions of the universe of other trace contaminants, whose presence will continue to be revealed at an escalating pace as the limits of analytical detection are driven lower and as the stream of new chemicals and nanomaterials are brought to market? If alterations to treatment technologies can be implemented to improve the removals of certain select PPCPs, might it be inevitable that these actions could serve to collaterally reduce the concentrations of trace contaminants whose presence is not yet known? Finally, often overlooked is that an emphasis on targeted monitoring can have the unintended consequence of preempting interest in expanding the identification of PPCPs occurring in the environment to those not previously targeted (see below: “Data Weaknesses or Liabilities").
Mining the Literature	While review articles continue to compile selected aspects of published data, exhaustive data mining from the published literature is extremely time consuming and seldom performed. Comprehensive compilations of existing information in a centrally available database would be enormously useful for: synthesizing new knowledge; informing data gaps and better targeting new research or monitoring efforts; improving measurement methodologies; assessing risk; avoiding duplication of effort or known dead ends;

	leveraging resources; improving the quality of data; and fostering a widespread dialog regarding the issues. Compiled data are needed not just for geographically based occurrence in waters, contaminant treatability, and toxicity, but also for other environmental compartments (e.g., landfills, biosolids, and sediments) and for various aspects of the larger issue, such as aquatic and vegetative bioconcentration and for drug disposal. Also useful would be the parallel compilation of negative data for those PPCPs ruled out as being present in samples above stated detection limits.
Data Gaps	Some notable gaps or liabilities in PiE research include the comparatively slight coverage of extent and scope of PPCPs occurrence in finished or point-of-use drinking water and landfills. The majority of APIs have never been targeted for environmental monitoring; instead, monitoring tends to focus on a core set of roughly a hundred or so of the thousands of APIs (or their degradates) from commercial use. Astonishingly light coverage is found of the occurrence (and bioconcentration/bioaccumulation) of environmentally derived residues of PPCPs in the tissues of aquatic organisms and in plants. Scant coverage exists of inventories of disposed medications and of the usage frequency of the methods of disposal. No research has focused on the potential for human effects and immune responses other than for model cellular studies. Standardized approach(es) for prioritizing individual PPCPs is needed for future work. Access to real-time, geographic API sales/usage data, which is largely proprietary in the U.S. or available only via subscription services, would greatly help in developing tools for prioritizing PPCPs to target for further

	studies or for informing the selection of monitoring targets, such as for the U.S. EPA's Contaminant Candidate List (http://www.epa.gov/ogwdw/ccl/index.html). Such usage data would also be extremely useful for validating predictive models for environmental fate. Four recent but uncommon examples of valuable data mining and synthesis are the compilations of occurrence and waste treatment data for various PPCPs [4-6] and ecotoxicity data [7].
Data weaknesses or liabilities	What percentage of PPCPs reported as identified in environmental matrices might have incorrect structural assignments? What are the assurances that we have an adequate understanding of what we are measuring? To what degree is the published literature possibly corrupted with incorrect structural assignments from mass spectral data? Are uniform publishing standards needed for ensuring that the structures of unknowns purportedly identified have indeed been appropriately confirmed (based upon standardized quality objectives) or, instead, tagged as tentatively identified? This problem has a corollary. Monitoring or chemical characterization studies often use a targeted approach that pre-selects analytes. Target analytes are often selected based on the results of prior studies. It is unknown how often the analyte selection process is based on prior work simply because of the availability of a workable analytical method as opposed to any consideration regarding risk. Chemicals previously identified then have a tendency to be selectively re-targeted for future monitoring - at the expense of ignoring analytes that have not yet been examined. How often is this pre-selection approach used to maximize the chances of obtaining positive results instead of to gain data for reducing uncertainty?

	Those contaminants not yet reported by monitoring tend to continue to be ignored because of an absence of data rather than data of absence; this points to the importance of populating databases with those API data falling below method detection limits (negative data). The targeted approach to monitoring can spawn biased data sets, populated preponderantly by particular, select chemicals that share the one biased commonality: they were simply known to be amenable to analysis. Are those PPCPs whose occurrence is repeatedly reported indeed the most prevalent or most important with respect to risk? Or perhaps others never monitored for might pose significant hazard? Is more emphasis needed on non-targeted analysis (attempts at comprehensive sample characterization), which could greatly expand the universe of PPCPs documented to occur in the environment? An associated question is whether PPCPs identified using discrete grab sampling (versus integrative sampling) adequately represent the types and quantities subject to real-world spatiotemporal variability; likewise, have conjugates of reversible metabolism been accounted for during monitoring as hidden reservoirs of the parent, aglycone APIs? An emerging trend in API design that could potentially further challenge structural identification is isotopic substitution. Deuterated analogs of APIs (as well as pesticides) have long been known to have altered pharmacokinetics/pharmacodynamics because of the kinetic isotope effect. Pharmacologic deuteration can yield APIs with greater stability and fewer side effects because of lower dose, metabolic switching, and reduced drug-drug interactions. An unknown with deuterated APIs would be whether environmental fate, transport, and effects would be altered. But more importantly, would a new analytical

	challenge emerge if the use of deuterated APIs [8] became established in medications? An API having one or multiple deuterated analogs would increase the numbers of potential analytes, hindering the identification of each other if they could not be effectively separated prior to detection.
Tying Effects to Exposure	A major problem with studies of low-level ecological exposure is the ever-increasing challenge of deconvoluting the occurrence of what might first appear to be an adverse effect in a certain (sub)population from the effect's frequency of incidence as natural, ambient background. Considerable evidence exists on the potential for low-dose effects from cellular and whole-organism controlled exposures at levels lower than the nanomolar or even picomolar ranges. But identifying and tying adverse consequences in non-target organisms exposed in real-world settings has met with limited success. To what extent do morphological abnormalities in aquatic organisms result from trace-level anthropogenic chemical exposures versus natural incidence? Similarly, to what extent can biological effects be masked or concealed by ambient incidence? Teasing the two apart is problematic and poses a primary barrier to establishing causality. Delayed-onset effects are a confounding factor in ascribing causality. Another important aspect to the risk potential for PPCPs is additive or interactive toxicity. This factor is greatly complicated by an MOA being shared with chemicals from other disparate groups unrelated to PPCPs - whether anthropogenic or naturally occurring. Such aggregate or cumulative exposure adds more complexity in ascribing cause and allocating risk. More attention is needed in design of controlled exposure experiments to ensure that the stressor levels mimic those actually encountered in the

environment; sometimes it seems that the need to report positive results (which might drive the need to use unrealistically high exposure levels) overrides the imperative to study exposure conditions that emulate real-world conditions (which stand a higher chance of not revealing observable effects).

With respect to effects, more comprehensive examination and survey is needed of the spectrum of possible subtle effects endpoints. Subtle effects, such as behavioral or immunological, can result from chronic low-level exposures from single or multiple PPCPs, each present below purported no-observed effects levels. Such exposures sometimes involve receptors that differ from those in humans; MOAs can change as the exposure levels are reduced, and dose-response linearity can vary greatly among chemicals [9]. Furthermore, the MOAs for many APIs are poorly understood, or the MOAs already established for therapeutic levels may not be relevant to the low levels encountered in the ambient environment. Multiple therapeutic endpoints or off-target effects can result from exposure to a single API because of the intricate interplay and cross-talk between signaling pathways - all of which are a complex function of dose, timing, and duration, among a host of other variables. With respect to ecological exposures, at what point does adaptive response give way to true toxicity - where disruption of homeostatic controls leads to adverse population-wide effects that cannot be sustained by a population?

Because of the difficulties surrounding low-level mixed-stressor studies, the continued exploration and application of the various omics and computational chemistry/toxicology could be a paradigm shifter. As for environmental monitoring, given the thousands of molecularly distinct APIs (multiplied further by

	isomers in racemates and by emerging aspects of drug design such as deuterated analogs, and further yet by multitudes of products from metabolism and other forms of transformation), is the ability or capacity to measure them all even necessary? Could carefully selected representative APIs (perhaps based on a suite of calculated properties) serve as surrogate proxies for the presence of many others? Alternatively, could monitoring be better served by switching from a targeted-chemical approach to one using biological endpoints - especially endpoints that serve to integrate the response from multitudes of stressors? Given the large numbers of PPCPs (although composing but an extremely small galaxy within the enormous universe of all potential chemical stressors), a major question is whether the long-established chemical-by-chemical approach to assessing hazard is sustainable? This challenge is indeed complex given the seemingly limitless exposure scenario combinations imparted by mixtures, coupled with the vast universe of chemicals for which toxicity studies do not even exist. Would a more feasible approach to assessing risk be to screen for (and then identify) the spectrum of bonafide chemical hazards in real-world samples via batteries of extremely rapid assays that use evolutionarily conserved toxicity-based pathways and other biology-based tools such as real-time gene-expression profiling? Endpoints of particular interest might be those based on mechanisms that are conserved across taxa; efflux pump inhibition and induction of the cellular stress response or apoptosis are but three examples of tests that could comprise a battery of assays - ranging from subcellular to systems-based. Results from these screens (akin to Whole Effluent Toxicity testing such as Toxicity Identification Evaluation or Toxicity Reduction

	Evaluation) could then be used to iteratively guide the identification of a complex sample's chemical constituents that embody the actual hazard. Should biological effects guide the comprehensive chemical characterization of exposure hazard rather than chemistry guiding an assessment of what effectively becomes an unknown portion of hazard? The latter, traditional approach requires assuming that the chemical(s) targeted for individual hazard testing are indeed the ones posing the hazard; this approach has obvious limitations when unregulated, emerging (or still unrecognized) chemicals impose the risk.
Aspects of Sources/Origins Important to Design of Stewardship Programs	Perhaps worth highlighting are some under-investigated aspects of origins or sources of exposure that might prove important to the design of stewardship programs. These include: the fate of APIs and creation of by-products during non-optimized incineration; the creation and fate of toxicologically significant by-products and transformation products during manufacture, wastewater treatment, metabolism/biotransformation, and physicochemical processes in the environment; the extent of occurrence and fate of PPCPs in biosolids and in recycled water, especially when applied to arable land; whether the nanomaterials used in the expanding field of nanomedicine/cosmetics pose risks once they enter the environment and undergo transformation (nanomaterials based on carbon structures are particularly problematic for chemical characterization because of their structural diversity); the extent to which plant-made pharmaceuticals pose a hazard if released to the environment; proactive environmental monitoring for new molecular entities at the time they are introduced into commerce; and apportioning the sources from which APIs gain entry to the environment (disposal, excretion, dermal transfer, bathing). An

aspect of sources sometimes overlooked is that some endogenous substances are also produced commercially and formulated in medications (17ß-estradiol being one example); unknown, however, is what portions of the ambient levels in the environment originate from commercial APIs versus endogenous synthesis.

Scenarios that might serve to increase existing real-world stressor levels also need to be assessed as integral aspects of the life cycles of PPCPs. Prominent among these are reduced flows of receiving streams, which increase the incidence of effluent-dominated streams, as well as reduced flows of treated sewage because of water conservation and increased sewer-use taxation. Both of these would serve to increase API concentrations in receiving streams.

Beginning only in 2007 was attention devoted to API residues that might occur in manufacturing waste streams - long discounted as probably not being a concern as a significant source. Recent monitoring data from manufacturing waste streams in India, however, now raise the question of whether this could be an overlooked localized source of APIs in receiving streams in the U.S. and other countries [10] .

A geographically networked early-warning water surveillance system could prove to be a very useful proactive approach for establishing baselines and detecting the emergence of not just new PPCPs, but any newly present pollutant. Such a scheme could be designed around change detection or chemical fingerprint anomalies - where rapid, high information-content chemical analysis could be used to establish baseline chromatograms showing the fingerprint of a sample in terms of the relative presence of all

	detectable chemicals. Resources could then be devoted to identifying only those chemicals newly detected in subsequent fingerprints (absent from baseline fingerprints archived from prior monitoring). These newly present chemicals could then be evaluated for potential importance for subsequent targeted tracking. Change-detection could be used to essentially justify ignoring all pre-existing chemicals unless changes in their relative concentrations happened to be of interest. This approach would be amenable to automation and could also prove to be an efficient means of tracking trends.
Dogma Masquerading as Knowledge	Several common assumptions or purported facts regarding PiE require probably require more attention and examination. These include the following, for which insufficient data exist to verify. Drug disposal is a significant source of APIs in the environment. Trace levels of antibiotics in the environment serve as a driver of selection for antibiotic-resistant human pathogens. Use of antibiotics in confined animal feeding operations poses a risk with regard to selection of antibiotic resistant bacteria and genetic transfer of resistance to human pathogens; note that the probable ubiquity of non-culturable bacteria greatly hampers solving this question. Malformations and sex alterations in wild aquatic populations are a result of endogenous and synthetic chemicals possessing hormonal activity (possible faulty suppositions regarding causality). Manufacturer waste streams are a minor source of APIs in the environment. Compared with conventional persistent organic pollutants, APIs are generally not subject to comparable bioconcentration because of their lower lipophilicity and ionizability (perhaps processes other than passive diffusion, such as active transport, can govern API uptake and bioconcentration). Finally, excipients do not need to be

	considered since they are not "active" ingredients.

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